CASE REPORTS

Refer to: Callaham M: Admission criteria for tricyclic antidepressant ingestion. West J Med 1982 Nov; 137:425-429

Admission Criteria for Tricyclic Antidepressant Ingestion

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COMPLEX AND SOMETIMES fatal complications make an overdose with a tricyclic antidepressant (TCA) one of the most difficult drug overdoses to manage. A further difficulty for a physician lies in assessing how much of the drug has been ingested by a patient who may appear clinically well. An illustrative case follows.

Report of a Case

A 38-year-old woman was brought to the emergency department at 9 PM stating she had taken a bolus of 20 to 30 of her mother's 50-mg desipramine tablets and an unknown quantity of alcohol two hours earlier. She had an empty bottle of the drug, and her mother confirmed the history. No other drugs were involved and the patient was not being treated with any other medications.

The patient was alert and oriented, and her speech was normal. Her blood pressure was 140/95 mm of mercury, the pulse rate was 125 per minute, respirations were 28 and temperature was not taken. On physical examination, the patient was noted to be obese; bowel sounds were present but hypoactive. The electrocardiogram (ECG) showed a sinus tachycardia with a rate of 125, normal axis, QRS duration of 0.10 seconds, QT interval of 0.35 to 0.38 seconds and PR interval of 0.18 seconds. Earlier ECG's were not available for comparison. The patient was given 30 ml of ipecac by mouth. Copious emesis resulted in the recovery of pill fragments. Charcoal and cathartics were not administered. Toxicologic studies done at this time showed a blood alcohol level of 0.04 percent, and a blood desipramine level of 0.02 μg per ml (therapeutic range 0.02 to 0.16 μg per ml). No traces of barbiturates, meprobamate, glutethimide, methyprylon, ethchlorvynol, chlordiazepoxide, diazepam or methaqualone were found. The laboratory uses a gas chromatography method with nitrogen-phosphorus detectors to test for TCA; the standard deviation of controls at 0.02 μg per ml is 0.0003 μg per ml. Blood gas and chemistry tests were not done.

The patient's clothing and belongings were removed and she was closely observed for the next six hours in the emergency department. Hourly ECG's remained the same as the first except for tachycardia, which gradually declined. Blood pressure stabilized at 120/90 mm of mercury. At 3 AM the patient was awake and alert, talking coherently and clearly, and was able to walk to the bathroom unassisted. Because she was constantly observed, and because all her personal belongings had been removed, it is exceedingly unlikely she ingested desipramine a second time in the emergency department. She was transferred to the psychiatric emergency department for evaluation; at this time her ECG was normal and pulse rate was 96 to 100 per minute. Upon entering psychiatric emergency at 3:30 AM her blood pressure was 120/90 mm of mercury, her pulse rate was 108 per minute, respirations 22 per minute and temperature 37.1°C (98.8°F). She was awake and alert but slightly unsteady on her feet. When seen by a psychiatrist at 5 AM her gait was unsteady, her speech was slurred and she was apparently having auditory hallucinations from time to time. She became increasingly agitated and fearful.

At 5:40 AM, three staff members lifted her onto a bed. Upon physical examination she was noted to have labored respirations, a blood pressure palpable at 60 mm of mercury and a weak and irregular pulse. Cardiopulmonary resuscitation was begun five minutes later. The first cardiac tracing, at 6 AM, showed asystole, which failed to respond to the usual advanced cardiac life support, and the patient was pronounced dead at 6:16 AM, 11 hours after ingestion of the drug.

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Submitted, revised, December 1, 1981.

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
TCA = tricyclic antidepressant

Autopsy findings were unremarkable except for the presence of hyperinflated lungs with sputum in the airways. This might have been caused by bronchial asthma, but the obstruction was not significant. The brain and heart were normal in all respects upon both gross and microscopic examination. The liver had some fatty metamorphosis. Analysis of a postmortem blood sample for all the drugs previously listed as well as for alcohol, showed only 8.6 μg per ml (8,600 ng per ml) of desipramine. Plasma levels of 1,000 ng per ml or more have been correlated with coma, seizures, arrhythmias, cardiac arrest and death.[1] A toxicologic test of the urine was negative for opiates, cocaine, amphetamines, methadone and propoxyphene.

Discussion

Delayed Complications

This case illustrates two of the major pitfalls in managing TCA overdose, particularly in an emergency department: delayed complications and inability to predict outcome by early clinical signs. Delayed complications may occur hours to days after ingestion of the drug, even after significant clinical improvement. The literature contains a number of such cases. Two infants who were admitted with coma and seizures, later awakened, and then collapsed and died 12 hours and 48 hours after TCA ingestion.[2,3] Reports of two young adults who were in coma when first examined are also interesting. One awoke and was alert for 12 hours after physostigmine was administered, then went into coma and a heart rate of 180 developed. The other awoke and responded to commands, but went into coma and a supraventricular tachycardia developed 57 hours after ingesting TCA's. Both survived.[4] Of two adults in coma when examined, one awoke and had a pulse rate of 90 per minute with a normal ECG except for incomplete right bundle branch block, yet at 50 hours after ingestion of TCA the patient collapsed, atrioventricular block and electromechanical dissociation developed and the patient died. The other patient not only awoke, but had a pulse rate of 82 per minute and a completely normal ECG, and was alert and cooperative when transferred to the ward. This 21-year-old collapsed on the toilet 94 hours after ingesting the drug, had a very slow heart rate with block and died. Autopsies of both patients were unremarkable.[5] Three other patients were admitted to hospital with major complications, had a cardiac arrest in the first 12 hours after admission but then died much later of other complications such as pneumonia.[6] Half of the patients in one large series had recurrence of tachycardia at 18 to 36 hours[7] and Sedal noted that half his TCA-overdose patients still had tachycardia on the sixth day after ingestion.[5] Most reviews note similar persistence of signs and symptoms, as well as an occasional worsening of the clinical condition after initial improvement.[7-11]

Causes of Delayed Complications

Delayed complications in TCA overdose may be due to several causes. The anticholinergic effects of these drugs slow peristalsis and absorption from the gut in overdose; intact pills have been recovered by lavage up to 18 hours after ingestion.[12,13] Absorption of TCA from the gut is dependent on the pH of intestinal contents; acid conditions hinder absorption.[14] Administration of cathartics may theoretically increase absorption by moving the drug through the alkaline small bowel, although this has never been studied. Once absorbed, the TCA is widely bound to tissue, creating a huge reservoir. Excretion is by renal and enterohepatic routes and is not only very slow but is affected by barbiturates, alcohol and smoking. Metabolism and half-life of these drugs is so variable that plasma levels vary up to 40-fold among persons receiving a given dose. This is among the largest of such differences known for any drug.[14,15] Half-life in overdose varies from 25 to 96 hours, with toxic levels persisting and often fluctuating for several days.[16,17] TCA protein binding fluctuates greatly with pH changes, including those induced by ventilatory status. Binding decreases from 98 percent at a pH of 7.5 to 90 percent at a pH of 7.0, drastically increasing supplies of the pharmacologically active drug. Arrhythmias induced by TCA's at a pH of 7.3 disappear promptly and completely when pH is raised to 7.5 by hyperventilation or administration of sodium bicarbonate.[18]

Predictive Factors

The second dilemma in TCA overdose is that the present state of the art does not allow physicians to predict which patients will have delayed

complications. As the case presented here vividly illustrates, initial absence of significant signs of poisoning such as coma, seizures, arrhythmia or hypotension does not rule out their later, unexpected development. Information about ingested doses is not only hard to obtain and unreliable, but also useless. Some patients have survived ingestion of 10 grams of amitriptyline while others have succumbed to 500 mg.[19,20] QRS duration of more than 0.10 seconds correlates well with plasma levels and major complications, and the general pattern is that the more prolonged the QRS, the higher the plasma level and the sicker the patient.[1] However, 25 percent of normal persons will have a QRS duration of 0.10 seconds and QRS duration has no predictive value, because it can change from minute to minute in concert with acid-base changes.[18] TCA plasma levels can be obtained, and they correlate with major complications.[1] However, this case illustrates also that unlike many other overdoses where relatively steady and predictable blood levels can be measured, plotted out on nomograms and used to predict toxicity, TCA levels can fluctuate greatly. For this reason, plasma levels of the drug have no predictive value. Rather than confirming or ruling out large ingestions, they serve only to document plasma levels at a given moment.

Significance of the Problem

The physician is thus left with no reliable means of predicting the outcome of the patient with only trivial signs of TCA poisoning. The case presented here is the first reported in the literature of an unexpected late death in a patient who initially had only trivial symptoms and signs; in the other six cases in the literature there were major complications such as coma and seizure which led to hospital admission. Conversations with other physicians have revealed several similar cases, and the true incidence of death is unknown. (Readers with experience of similar cases are invited to communicate details to the author.)

In one recent study, 40 percent of all TCA overdose patients had only minor symptoms, 73 percent of pediatric cases had symptoms too minor to warrant treatment and 40 percent of pediatric cases had no symptoms at all.[21] In recent years, 2,657 emergency visits involving amitriptyline alone, and 340 deaths in which amitriptyline contributed, were reported each year for the 30 percent of the United States population monitored by the Drug Abuse Warning Network (DAWN).[22] Thus, thousands of patients each year are seen in emergency departments with only trivial symptoms from TCA overdose, and decisions about their need for admission to hospital must be made.

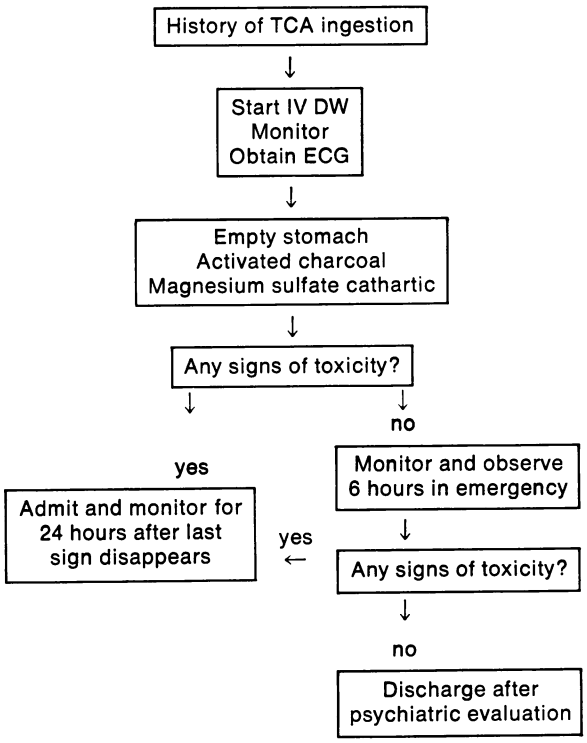

Figure 1.—Initial management strategy in tricyclic antidepressant ingestion.

Suggested Admission Criteria

Definition of the admission criteria for these "minor" ingestions has seldom been addressed in the literature. Rumack recommended that patients without tachycardia (defined as a rate of 110 per minute or greater) or "other life-threatening problems" not be admitted.[23] Such a guideline would not lead to the admission of patients such as this one. Crome and Newman suggested that patients with a history of TCA ingestion, but no symptoms, be observed in the emergency department for six hours and then discharged if still symptom-free.[21] The initial tachycardia of the patient reported here would have qualified her for admission under these criteria.

The protocol recommended by the author is summarized in Figure 1. All patients giving a history of TCA ingestion of any kind should receive an intravenous line at a keep-open rate, have cardiac monitoring done and receive an ECG in addition to the regular physical examination.

They then should have stomachs emptied and receive activated charcoal, which binds the drug in the gut. Repeated doses of charcoal at one-hour intervals bind the portion of the drug excreted in the bile and gastric juices and are even more effective.[24] This important measure was omitted in this patient, and might have prevented the later fatal absorption of the drug. Cathartics are routinely recommended, although their effectiveness has never been studied in any overdose, and they might theoretically increase absorption.[25] Considering the long time the drug may remain unabsorbed in the hypotonic gut, however, it seems logical to bind it with a dose of charcoal and then hasten elimination with cathartics. This step also was omitted in this patient's care.

If on first examination patients have *any* of the signs of toxicity listed in Tables 1 through 3, they should immediately be admitted to hospital. Tachycardia and QRS prolongation are particularly important signs. Most of the less severe of these signs have been reported occasionally as a side effect of therapeutic TCA doses, so acute overdose may be harder to diagnose in those patients receiving ongoing therapy. However, the incidence of side effects is not high enough to create confusion in most cases and when in doubt the patient should be admitted. In the hospital, the patient should be monitored electrocardiographically for at least 24 hours after the disappearance of the last sign because 98 percent of all signs of cardiotoxicity appear within that time period.[23,26] If patients have no signs of toxicity on arrival in the emergency department, they should be monitored and observed for at least six hours. If any signs or symptoms develop, no matter how minor, they should be admitted. If not, they may be discharged after appropriate psychiatric consultation.

This protocol should result in the admission of virtually all potentially fatal cases to the hospital, where cardiotoxicity can be detected early and treated aggressively. It will also result in the admission of a number of trivial cases that do not really need such care. However, the consequences of missing those few who truly need admission are so disastrous that until the true incidence of delayed complications in "trivial" overdoses can be accurately determined, or until accurate predictors of outcome are developed, a very low-risk strategy should be employed.

TABLE 1.—*Peripheral Signs of Tricyclic Antidepressant Toxicity (Peripheral Anticholinergic Syndrome)*

Tachycardia (100 or greater)*
Hypertension
Fever
Mydriasis
Dry red skin
Decreased bowel sounds
Urinary retention
Respiratory depression

*In a quietly resting patient, a pulse rate of 90 per minute or greater should be considered suspicious.

TABLE 2.—*Central Nervous System Signs of Tricyclic Antidepressant Toxicity*

Disorientation
Agitation
Hallucinations
Myoclonic jerks
Coma
Seizures
Pyramidal signs
clonus
Babinski present
hyperreflexia

TABLE 3.—*ECG Abnormalities in Tricyclic Antidepressant Overdose*

ST and T wave changes
Prolonged QT interval
Prolonged PR interval
QRS greater than 0.10 seconds*
Bundle branch blocks
Atrioventricular conduction blocks (first degree, second degree or complete)

*Correlated with high plasma levels and major complications.

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Refer to: Baxi SC, Dailey GE III: Hypervitaminosis A: A cause of hypercalcemia. West J Med 1982 Nov; 137:429-431

Hypervitaminosis A

A Cause of Hypercalcemia

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IN THE PRESENT CLIMATE of increased health and nutrition consciousness, physicians commonly see patients taking a host of different vitamin and mineral supplements, frequently in pharmacologic doses. One lipid soluble vitamin still available in large unit doses and in widespread use is vitamin A. Complications of hypervitaminosis A have been recognized for a number of years. However, hypervitaminosis A has been infrequently recognized as a cause of hypercalcemia. We wish to report the case of a patient who had pronounced hypercalcemia, rapidly reversible after discontinuation of large doses of vitamin A.

Report of a Case

A 29-year-old woman, a part-time employee of a health food store, presented with a four-week history of illness. She had consulted an ophthalmologist for dryness and irritation of her eyes, which prevented her from wearing contact lenses. She also noted redness and irritation of her gums and tongue, and fissures at the corners of her mouth (cheilosis). There was dryness and itching of her skin, as well as generalized weakness and malaise for approximately two weeks. Headache had begun one week before admission, it was occipital in location and moderately severe. She was forced to give up jogging because of muscle aches and pains, particularly in the anterior lower legs. Nausea, vomiting and pronounced weakness had been present for four to five days before her presentation.

Medications

On questioning, it was found that she had taken two tablets per day of a combination vitamin preparation, which contained 25,000 units of vitamin A and 100 units of vitamin D. She had taken two tablets per day for at least three months.

Thinking her dry eyes and mouth may be a manifestation of vitamin A deficiency, she took an additional 50,000 units of vitamin A a day for one week before presentation. She was taking no other medications. Specifically, there were no other sources of vitamin D, calcium supplementation or diuretics.

Physical Examination

The patient appeared moderately ill and weak. Height was 161 cm, weight 52.7 kg. Temperature was 37°C, pulse 52 and blood pressure 110/70 mm of mercury, with no orthostatic drop. There was cheilosis around the mouth and some erythema of the gums and mouth. There was no visible keratoconjunctivitis. The thyroid was normal in size. Findings on examination of the lungs, heart, breasts, abdomen and pelvis were within normal limits. The abdomen was soft. Liver span was approximately 8 cm. There was no palpable splenomegaly. The deep tendon reflexes were symmetrical and normal in timing.

Laboratory Data

The serum calcium concentration was reported to be notably elevated at 14.4 mg per dl. The serum phosphate level was 3.6 mg per dl. Other laboratory data included a leukocyte count of 4,500 with normal differential. Hemoglobin was 10.9 grams per dl. Hematocrit was 30.6 percent. Erythrocyte sedimentation rate was 43 mm per hour. Serum creatinine was 0.9 mg per dl. Pro-

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Submitted, revised, September 14, 1981.

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